DEPARTMENT OF HEALTH AND HUMAN SERVICES

DHB

Food and Drug Administration

Display Date 7-6-03
Publication Date 7-17-03
Certifier Reese

21 CFR Part 348

[Docket No. 78N–0301]

RIN 0910–AA01

External Analgesic Drug Products for Over-the-Counter Human Use; Reopening of the Administrative Record and Amendment of Tentative Final Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is reopening the administrative record for the rulemaking for over-the-counter (OTC) external analgesic drug products to accept comments and data concerning OTC external analgesic drug products that have been filed with the Division of Dockets Management, FDA, since the administrative record officially closed. FDA is also amending the tentative final monograph (TFM) (proposed rule) to clarify the status of patch, plaster, and poultice dosage forms for OTC external analgesic drug products. FDA is providing for the administrative record to remain open for 90 days to allow for public comment on the comments and data being accepted into the rulemaking and on the status of patch, plaster, and poultice dosage forms for OTC external analgesic drug products. This action is part of FDA's ongoing review of OTC drug products.

DATES: Submit written or electronic comments and data by [*insert date 90 days after date of publication in the* **Federal Register**]. See section IX of this

document for the effective date of any final rule that may be published based on this proposal.

ADDRESSES: Submit written comments and data to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http://www.fda.gov/dockets/ecomments.*

FOR FURTHER INFORMATION CONTACT: Gerald M. Rachanow, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2307.

SUPPLEMENTARY INFORMATION:

I. Background

FDA has on numerous occasions received new data and information bearing on OTC drug panel reports and proposed monographs after the closing of the administrative record in a rulemaking proceeding. Under § 330.10(a)(7)(iii) (21 CFR 330.10(a)(7)(iii)), new data and information may be submitted within 12 months after publication of a TFM. Within 60 days after this 12-month period ends, comments on the new data and information may be submitted (see § 330.10(a)(7)(iv)). Under § 330.10(a)(10)(i), the administrative record closes at the end of this 60-day period.

In the **Federal Register** of February 8, 1983 (48 FR 5852), FDA published the TFM on OTC external analgesic drug products for OTC human use. The administrative record for this TFM closed on April 9, 1984. The administrative record for this rulemaking was last reopened on November 19, 1997 (62 FR 61710) to include safety and effectiveness data on OTC vaginal douche drug product ingredients for external analgesic uses (e.g., povidone-iodine for the relief of minor vaginal itching and irritation) and closed on February 17, 1998.

Under § 330.10(a)(7)(v), new data and information submitted after February 17, 1998, prior to the establishment of a final monograph (FM), are considered a petition to amend the monograph and are to be considered only after a FM has been published unless the agency finds that good cause has been shown that warrants earlier consideration. Further, under § 330.10(a)(10)(ii), FDA shall make all decisions and issue all orders under § 330.10 in the FM solely on the basis of the administrative record and shall not consider data or information not included as part of the administrative record.

FDA has received new data and information submitted to the external analgesic rulemaking after the administrative record closed on April 19, 1984. In some cases, interested persons submitted a petition to reopen the record. In other cases, they submitted new data and information to the Division of Dockets Management as comments on the TFM. A number of the petitions and comments submitted to the TFM contain new data on proposed nonmonograph (Category II and Category III) ingredients and on external analgesic active ingredients applied in a patch, plaster, or poultice dosage form.

II. Reopening of the Administrative Record

Because these data are relevant to the final classification of these ingredients in the FM, FDA has determined that good cause exists to consider these new data and information in developing the FM for these products. By this document, FDA announces that it is treating all of these submissions, received after the administrative record closed, as petitions to reopen the administrative record, and is granting the petitions by allowing the new data and information contained therein to be included in the administrative record for the rulemaking for OTC external analgesic drug products. Accordingly, the agency is reopening the administrative record for this rulemaking to accept

data and information previously submitted to the Division of Dockets Management into the administrative record and to provide interested persons an opportunity to submit comments on these data and information prior to the closing of the record.

III. Status of Patch, Plaster, and Poultice Dosage Forms for OTC External Analgesic Drug Products

After the TFM was published on February 8, 1983, FDA received a petition (Ref. 1) to amend portions of the TFM to add poultice or plaster dosage forms only for the counterirritant ingredients in proposed § 348.12, specifically for the ingredients methyl salicylate; camphor; menthol; and capsicum. This petition led FDA to review the report of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (the Panel) (44 FR 69768, December 4, 1979), the TFM for OTC external analgesic drug products, available data, marketing history, and the current market for OTC counterirritant ingredients in topical drug products used in poultice and plaster dosage forms.

FDA found that the Panel discussed poultices and plasters only in its discussion of allyl isothiocyanate (oil of mustard) (44 FR 69768 at 69791 and 69792) and stated its concern that used as a poultice, the inflammatory action caused by allyl isothiocyanate may go beyond erythema to vesication. It was the Panel's opinion that although the actual number of adverse effects to external use of mustard preparations was relatively low, care should be taken to assure that safety is maintained through adequate packaging, labeling, and application. The low incidence of adverse reactions the Panel discussed (44 FR 69768 at 69791) was for an ointment dosage form (Ref. 2) and not for a plaster or poultice (a soft, moist mass about the consistency of cooked cereal, spread between layers of muslin, gauze, or towels and applied hot to a given

area in order to create moist local heat or counterirritation). The Panel did briefly discuss mustard plaster, National Formulary IX , but did not include a plaster dosage form in its recommended dosage for this ingredient (44 FR 69768 at 69792).

The Panel did not discuss plaster or poultice dosage forms for any other counterirritants, although articles from standard texts in some of the submissions to the Panel indicated that capsicum has been used in a plaster dosage form (Ref. 3). There was one submission to the Panel for a medicated poultice dressing containing methyl salicylate, salicylic acid, and eucalyptus oil as active ingredients (Ref. 4). Although the Panel recommended a Category I classification for methyl salicylate, it did not discuss the submission related to the use of this ingredient as a poultice or plaster. The submission did not contain any controlled clinical evaluations to support safety and effectiveness of the combination drug product or for the specific contribution of the individual active ingredients. The product's safety and effectiveness were based on its performance for 80 years. At that time, FDA surveyed several standard texts that listed currently marketed topical drug products containing counterirritants and did not find any plaster or poultice dosage forms listed therein.

FDA stated (Ref. 5) that in order for poultice and plaster dosage forms to be generally recognized as safe and effective and to develop any additional labeling that may be needed for such dosage forms, it is necessary to obtain more information, specifically:

1. The safe and effective concentration of the drug ingredient(s), especially under the occlusion of a plaster.

2. Data on percutaneous absorption under occlusion.

3. The length of contact time that it is safe to leave the poultice or plaster on the skin; how often the plaster or poultice needs to be changed for effective use.

4. The frequency of application that is considered safe and effective.

5. Whether or not directions and a warning are necessary regarding checking the area at specified intervals for erythema to prevent blistering, and what time intervals are recommended.

6. The age groups for whom poultices and plasters are recommended for safe use.

7. Labeling of currently marketed products.

FDA's detailed comments are on file in the Division of Dockets Management (Ref. 5).

Since that time, FDA has received a number of submissions on external analgesic counterirritant active ingredients in a plaster dosage form (Refs. 6 through 31). The submissions have included protocols and data to establish safety and effectiveness of the plaster/patch dosage forms. FDA has commented on the protocols and data, but has not found the information sufficient to support the safety and effectiveness of these dosage forms (Refs. 32 through 44). Further, FDA is not aware of sufficient data to classify any OTC external analgesic active ingredient in a patch, plaster, or poultice dosage form as Category I. Accordingly, FDA is classifying all OTC external analgesic ingredients in a patch, plaster, or poultice dosage form in Category III (more data needed). FDA is proposing to amend the introductory language in §§ 348.10 and 348.12 to include the following language at the end of the currently proposed language, to read as follows: "The active ingredients of the product consist of any of the following, within the established concentration

for each ingredient, but not for use in a patch, plaster, or poultice dosage form." FDA will revise this language if any of these active ingredients are found acceptable for use in one of these dosage forms.

IV. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation).

FDA believes that this proposed rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. FDA has determined that the proposed rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order. As explained later in this section, FDA believes that the proposed rule, if finalized, will not have a significant economic impact on a substantial number of small entities. The Unfunded Mandates Reform Act does not require FDA

to prepare a statement of costs and benefits for this proposed rule, because the proposed rule is not expected to result in any 1-year expenditure that would exceed $100 million adjusted for inflation. The current inflation adjusted statutory threshold is about $110 million.

The purpose of this proposed rule is to determine the monograph status of patch, plaster, and poultice dosage forms for external analgesic drug products for OTC human use. This proposed rule indicates that these dosage forms have not been determined to be generally recognized as safe and effective for any OTC external analgesic drug products at this time.

Manufacturers who wish to market these types of products for external analgesic active ingredients need to provide additional safety and effectiveness data to FDA before the FM for these products is established. If adequate safety and effectiveness data are not provided, FDA will not include these types of dosage forms for external analgesic active ingredients in the FM, to be published in a future issue of the **Federal Register**, and any currently marketed products will no longer be able to be marketed when the FM becomes effective, unless they are the subject of an approved new drug application.

FDA estimates that there is a limited number of OTC patch, plaster, and poultice external analgesic drug products currently in the marketplace. Reformulation will not be possible if these dosage forms are not included in the FM. Thus, manufacturers of these products may incur a loss of revenue. However, these manufacturers may be able to replace these products with other products that contain monograph ingredients in the dosage forms currently proposed for inclusion in the FM, e.g., creams, lotions, ointments. Manufacturers will not incur any costs related to proving safety and effectiveness of the active ingredients in these proposed monograph dosage

forms. Based on the lack of adequate scientific information on external analgesic active ingredients in patch, plaster, and poultice dosage forms, FDA does not believe that there are any significant alternatives to the proposed rule that would adequately provide for the safe and effective use of these specific OTC drug products.

Under the Regulatory Flexibility Act, if a rule has a significant impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of a rule on small entities. This proposed rule would exclude patch, plaster, and poultice dosage forms from the final monograph for OTC external analgesic drug products. A few entities that currently market these products may incur significant impacts if these products are not included in the final monograph. However, as only a limited number of small firms market these products in the dosage forms that may not be included in the FM, FDA does not believe that this proposed rule will impose a significant economic burden on affected entities. Thus, this economic analysis, together with other relevant sections of this document, serves as FDA's initial regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

FDA invites public comment regarding any substantial or significant economic impact that this rulemaking would have on manufacturers who market these products. Comments regarding the impact of this rulemaking on such manufacturers should be accompanied by appropriate documentation. FDA is providing a period of 90 days from the date of publication of this proposed rulemaking in the **Federal Register** for comments to be developed and submitted. FDA will evaluate any comments and supporting data that are

received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

V. Paperwork Reduction Act of 1995

This proposed rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VI. Environmental Impact

The agency has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency tentatively concludes that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

VIII. Request for Comments

FDA is reopening the administrative record for a period of 90 days for comments, new data, and information to be submitted. Interested persons have already had an opportunity to submit comments, objections, or requests for an oral hearing on the TFM. Therefore, any comments at this time should only address the data and information submitted to the administrative record after

April 9, 1984, and should specifically identify the data and information on which the comments are being provided. In addition, only new information related to the submissions being included in the administrative record at this time should be submitted. Any data and information previously submitted to this rulemaking need not be resubmitted. In establishing an FM, FDA will consider only comments, data, and information submitted prior to the closing of the administrative record following this current reopening.

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments to *http://www.fda.gov/dockets/ecomments* or three paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

IX. Proposed Effective Date

FDA is proposing that any final rule that may issue based on this proposal become effective 12 months after its date of publication in the **Federal Register**.

X. References

The following references are on display in the Division of Dockets Management (see **ADDRESSES**) under Docket No. 78N–0301 and may be see by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Comment No. CP6.

2. OTC vol. 060051.

3. OTC vol. 060033.

4. OTC vol. 060052.

5. Comment No. LET39.

6. Comment No. C109.

7. Comment No. CP8.

8. Comment No. SUP8.

9. Comment No. LET46.

10. Comment No. RPT4.

11. Comment No. LET51.

12. Comment No. C111.

13. Comment No. LET57.

14. Comment No. LET66.

15. Comment No. PR1.

16. Comment No. PR2.

17. Comment No. CR9.

18. Comment No. CP13.

19. Comment No. C116.

20. Comment No. PR3.

21. Comment No. LET71.

22. Letter from M. Rapaport to D. Bowen, FDA, dated May 1, 1997.

23. Letter from M. Rapaport to L. Katz and S. Aurecchia, FDA, dated May 28, 1997.

24. Telefax from J. L. Boren, Argus Research, Inc., to M. Rapaport, dated June 17, 1997.

25. Letter from M. Rapaport to S. Aurecchia, FDA, dated June 23, 1997.

26. Letter from M. Rapaport to L. Katz and S. Aurecchia, FDA, dated July 1, 1997.

27. Comment No. LET84.

28. Letter from M. Rapaport to E. Yuan, FDA, dated April 1, 2000.

29. Comment No. SUP9.

30. Comment No. SUP10.

31. Comment No. SUP11.

32. Comment No. LET49.

33. Comment No. LET50.

34. Comment No. LET55.

35. Comment No. LET61.

36. Comment No. MM9.

37. Comment No. LET67.

38. Comment No. LET68.

39. Comment No. LET69.

40. Comment No. LET70.

41. Comment No. PDN2.

42. Comment No. LET85.

43. Comment No. MM10.

44. Comment No. LET86.

List of Subjects in 21 CFR Part 348

Labeling, Over-the-counter drugs.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 348 (as proposed in the **Federal Register** of February 8, 1983 (48 FR 5852)) be amended as follows:

PART 348—EXTERNAL ANALGESIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

■ 1. The authority citation for 21 CFR part 348 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

■ 2. Section 348.10 is amended by revising the introductory text to read as follows:

§ 348.10 Analgesic, anesthetic, and antipruritic active ingredients.

The active ingredients of the product consist of any of the following, within the established concentration for each ingredient, but not for use in a patch, plaster, or poultice dosage form:

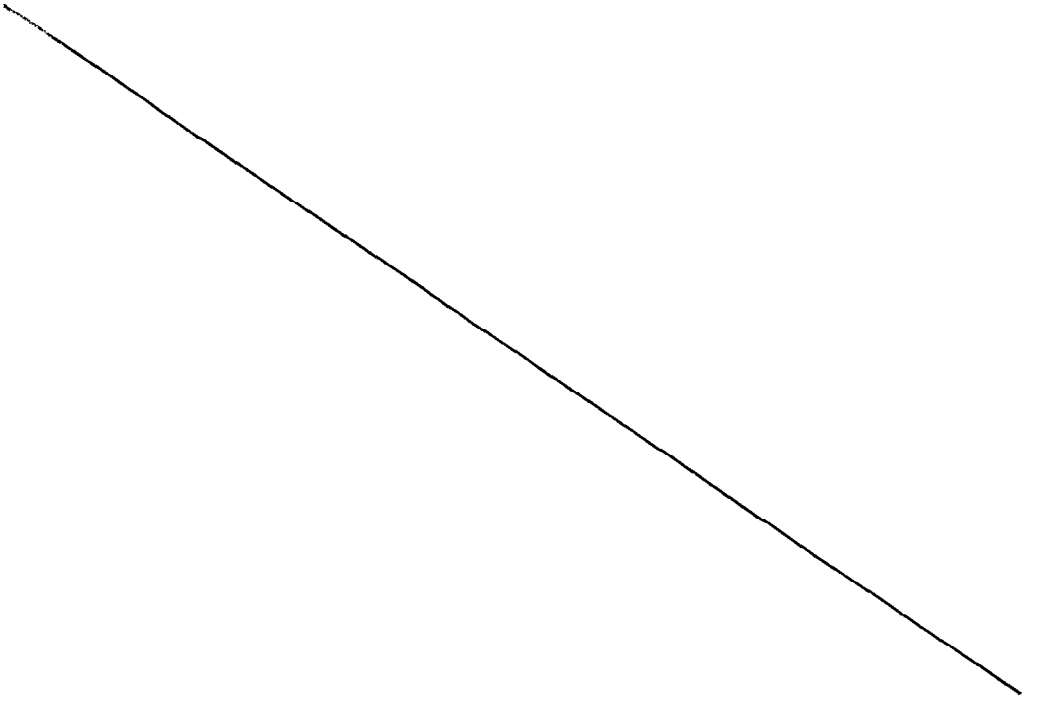
* * * * *

■ 3. Section 348.12 is amended by revising the introductory text to read as follows:

§ 348.12 Counterirritant active ingredients.

The active ingredients of the product consist of any of the following, within the established concentration for each ingredient, but not for use in a patch, plaster, or poultice dosage form:

* * * * *



Dated: 7/7/03

July 7, 2003.

cd0324

Jeffrey Shuren,
Assistant Commissioner for Policy.

[FR Doc. 03–????? Filed ??–??–03; 8:45 am]

BILLING CODE 4160–01–S